REMARKS

Claim 1 has been amended. Claims 1-9 are now pending in this application. Support for the amendments is found in the existing claims and the specification as discussed below. Accordingly, the amendments do not constitute the addition of new matter. Applicant respectfully requests the entry of the amendments and reconsideration of the application in view of the amendments and the following remarks.

Rejection under 35 U.S.C. § 103(a)

Claims 1-9 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Lee, et al. (WO 02/072875A1) in view of Crockett, et al. (2001).

The Office Action states that Lee, et al. teach a combination of mutated gene sequences involved in insulin secretory function, including S20G amylin. Lee, et al. do not described a melting curve analysis using a probe labeled with a fluorescent dye. Crockett, et al. is cited for this teaching.

In response to the Examiner's comment in the Final Office Action that "Claims 1 and 7 do not require the 5' end of the probe to correspond to the nucleotide at nucleotide number 247..." (Final Office Action, page 7, item 3, first paragraph), Applicant has amended claim 1 to recite specifically that "the nucleic acid probe has a nucleotide sequence complementary to a nucleotide sequence consisting of nucleotide number 247 of SEQ ID NO: 1 and 13 to 30 nucleotides 5' to nucleotide number 247 of SEQ ID NO:1". Applicant requests reconsideration of the arguments presented previously in light of the amendment. These arguments are restated below.

As presented in the previous response, while Lee, et al. disclose the nucleotide sequence with the S20G mutation which covers the sequence complementary to the nucleic acid probe of the present invention (Figure 5), Lee, et al. do not specify the nucleotide at nucleotide number 247 and do not recognize that nucleotide number 247 should correspond to the 5' end of any probe.

As previously argued, among the many cytosines that can be labeled, the cytosine complementary to guanine at nucleotide number 247 of SEQ ID NO: 1 is critical. When the probes of the present invention, having a 5' cytosine and complementary to guanine at nucleotide number 247 were used (Figure 2) changes in fluorescence intensity that could be analyzed in Tm

analysis were obtained. However, as shown in Figure 1, when probes having a cytosine end but complementary to guanine at positions other than position 247 were prepared, changes were not observed (as discussed in the present specification at page 12, lines 7-10 from bottom). The importance of the guanine at position 247 at the 5' end of the probe could not have been predicted based upon the cited references. There was no reasonable expectation of success that merely combining the teachings of the two cited references would lead to the claimed invention. Accordingly, the two cited references taken as a whole do not teach or suggest the invention claimed.

Furthermore, it was not expected that the IAPP S20G mutation could be detected based upon the results of the Tm analysis (Figures 3 and 4). Quantification of the mutant type DNA and determination of the ratio of wild type DNA and mutant type DNA were (Figure 5) were also unexpected.

The Examiner's second point in the "Response to Arguments" section of the last Office Action (page 7, item 3, paragraph 2) is that one of skilled in the art would have arrived at Applicant's probe through routine experimentation based upon Crockett, et al..

In response, Crockett, et al. describe a 25% decrease in fluorescence of 5'-labeled probes with a G at the first position of the 3'dangling end. Figure 7 and 8 of Crockett, et al. suggest that a G at the first position of the 3'dangling end is important. However, Crockett, et al. do not teach or suggest the importance of positioning the probe in the target sequence. That is, Applicant, in contrast to Crockett, et al., asserts that not all G positions are equivalent. As mentioned above, Figure 1 of Applicant's specification shows that probes having a cytosine, but complementary to guanine at positions other than 247, were not effective and could not be used for Tm analysis.

Furthermore, the following experiment from JP 2005-261354 (Attachment A, partial translation in three pages) evidences that there are no hard and fast rules in the design of effective probes. The result in Figure 2 (Example 2) in JP 2005-261354 (partial translation attached) contradicts Figure 7 and 8 of Crockett, et al. Figure 2 uses the probe in Table 3 (i.e. the probe which has a G at the 3'dangling end) and Figure 2 suggests that a G at the first position of the 3' dangling end was not effective for quenching. Specifically, when the nucleic acid probe of SEQ ID NO: 2 hybridized to the target sequence of SEQ ID NO: 7 (Table 3), the fluorescence was not quenched. But the fluorescence was quenched when the duplex of the nucleic acid probe and the

target sequences was heated and dissociated (i.e. the fluorescence was emitted while the nucleic acid probe of SEQ ID NO: 2 hybridized to the target sequence of SEQ ID NO: 7). Since the fluorescence of the probe for quantitative PCR is designed to be quenched on hybridization, the probe is not effective. The G at the first position of the 3' dangling end was not sufficient for quenching in this case.

On the other hand, in the present invention, the fluorescence was quenched only when two Gs exist at positions 0 and 1 (the first position of the 3' dangling end), and Gs other than the two Gs (nucleotides no. 247 and 248) were not effective for quenching.

One of ordinary skill in the art would have never expected from Crockett, et al. that the two Gs at position 0 and 1, which correspond to nucleotides no. 247 and 248 in the present invention, are essential. Based upon Crockett, et al. one of ordinary skill in the art would have expected that any G in the target sequence could be used as the basis to design an effective probe that would show a fluorescence change upon hybridization. However, as shown by Applicant's specification and the Attached translation of JP 2005-261354, this is not the case. Accordingly, Applicant respectfully submits that the present claims as amended are patentable over Lee, et al in combination with Crockett, et al.

In view of Applicant's amendments and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, the Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. The Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

Co-Pending Applications of Assignee

Applicant wishes to draw to the Examiner's attention to the following co-pending applications of the present application's assignee. Application in **BOLD** is the present application.

Serial Number	Title	Filed
09/817,251	METHOD FOR STIRRING LIQUIDS	03/27/01
10/466,453	QUANTITATIVE ANALYZING METHOD AND QUANTITATIVE ANALYZER USING SENSOR	12/02/03
10/481,397	INFORMATION COMMUNICATION SYSTEM	12/19/03
10/483,205	ADJUSTABLE LANCING DEVICE	01/07/04
10/493,919	TEST APPARATUS	04/27/04
10/862,465	METHOD AND IMPLEMENT FOR OPENING HOLE IN SOFT MATERIAL	06/08/04
10/498,782	SAMPLE MEASURING DEVICE	06/10/04
10/533,601	ANALYTICAL TOOL	04/29/05
10/545,852	METHOD OF DETECTING CHLAMYDIA TRACHOMATIS AND KIT THEREFOR	08/17/05
10/547,354	DNA AMPLIFICATION METHOD AND KIT THEREFOR	08/29/05
11/220,622	SUPPLEMENT FOOD FOR LOW BLOOD GLUCOSE RECOVERY	09/08/05
10/553,576	METHOD OF DETECTING OR QUANTITATIVELY DETERMINING MITOCHONDRIAL DNA 3243 VARIATION, AND KIT THEREFOR	10/17/05
10/536,822	METHOD AND APPARATUS FOR CONCENTRATION AND PURIFICATION OF NUCLEIC ACID	10/18/05
10/533,509	METHOD OF DETECTING B3 ADRENALINE RECEPTOR MUTANT GENE AND NUCLEIC ACID PROBE AND KIT THEREFOR	10/18/05
10/553,614	**METHOD OF DETECTING PANCREATIC ISLET AMYLOID PROTEIN MUTANT GENE AND NUCLEIC ACID PROBE AND KIT THEREFOR**	**10/18/05**
10/553,376	METHOD OF ISOLATING NUCLEIC ACIDS, AND KIT AND APPARATUS FOR NUCLEIC ACID ISOLATION	10/19/05
10/536,829	DEVICE FOR PRETREATING SPECIMEN	10/31/05
10/550,671	PROCESS FOR PRODUCING GLUCOSE DEHYDROGENASE	11/09/05
11/587,333	MUTANT GLUCOSE DEHYDROGENASE	10/19/06
11/712,307	METHOD FOR DETECTING TARGET NUCLEIC ACID	02/27/07

CONCLUSION

In view of Applicants' amendments to the claims and the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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ATTACHMENT A

Partial translation of JP 2005-261354 A

[Example 1]

[0027]

Requirement study 1

A nucleic acid probe consisting of an oligonucleotide labeled with the fluorescent dye (TAMRA) at its end, a target sequence having a sequence which is complementary to the nucleic acid probe, and an oligonucleotide (artificially synthesized oligo) having the sequence complementary to the nucleic acid probe wherein 1, 2, or 3 nucleotides corresponding to those at fluorescent dye-labeled end of the nucleotide probe do not match the nucleic acid probe, were synthesized (Table 2). In addition, the (P) of the 3' terminal shows that phosphorylation was carried out (the same applies to subsequent tables).

[0028]

The solution for fluorescence measurement which has the composition shown in Table 2 was prepared, temperature was changed on the conditions shown in Table 2 using Smart Cycler System (product made from Cepheid), and fluorescence was measured.

[0029]

[Table 2]

Table 2

The nucleic acid probe

5T-CYP2C19-3-wt-R4-22-C (TAMRA)-CTTGGCCTTACCTGGATCCAGG-(P) (SEQ ID NO:1)

The target sequence(artificially synthesized oligo)

2C19-3-F-wt-3-IMS AGCACCCCCTGGATCCAGGTAAGGCCAAGTTTTTTGCTTC (SEQ ID NO:7)

2C19-3-F-wt-4-IMS AGCACCCCCTGGATCCAGGTAAGGCCAACTTTTTTGCTTC (SEQ ID NO:8)

2C19-3-F-wt-5-IMS AGCACCCCCTGGATCCAGGTAAGGCCATCTTTTTTGCTTC (SEQ ID NO:9)

2C19-3-F-wt-6-IMS AGCACCCCCTGGATCCAGGTAAGGCCTTCTTTTTTGCTTC (SEQ ID NO:10)

The boxed region corresponds to the nucleic acid probe sequence and underlined nucleotides are mismatched.

The composition of a solution for fluorescence measurement (final concentration)

The artificially synthesized oligo	400nM
The nucleic acid probe	200nM

Glycerol	10%
Gene Taq Universal Buffer (Nippon gene corp.)	1×
Final volume	25 μL

Condition for fluorescence measurement
Temperature 45～85℃(measured by every 0.5℃)
Exitation wave length 527nm～555nm
Fluorescence measurement wave length 565nm～605nm

[0030]

The result is shown in Figure 1. Figure 1 shows the curve wherein the measured values were amended by subtracting the numerical difference so that the value in the range where the inclination is constant becomes the same as control at the side of the high temperature range (after probe dissociation).

[0031]

In the case of 1, 2, or 3 nucleotide mismatch, the rapid fall of fluorescence intensity was observed near the melting temperature. Although changes of fluorescence intensity became larger in order of 3, 2, and 1 base mismatch, while in the case of the perfect match, the fall of fluorescence intensity was not observed.

[0032]

The quenching probe, which is designed so that a plurality of base pairs of the probe-the nucleic acid hybrid form at least one G-C pair at its end when the probe whose end is labeled with the fluorescent dye hybridized to the target nucleic acid, is known (JP2002-119291A). It was presumed that quenching was observed by the interaction of the fluorescent dye and the guanine of the target sequence, since the nucleic acid probe used in this Examples fulfills this condition.

[Example 2]

[0033]

Requirement study 2

In order to confirm a presumption in Example 1, fluorescence was measured as in Example 1, except that the nucleic acid probe which does not fulfill the conditions of a quenching probe, and the artificially synthesized oligo (refer to Table 3) corresponding to the nucleic acid probe were prepared and used.

[0034]

[Table 3]

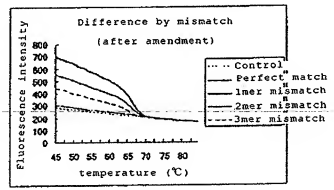
The nucleic acid probe
5T-CYP2C19-3wt-R4T21 (TAMRA)-TTGGGCCTTACCTGGATCCAGG-(P) (SEQ ID NO:2)

The target sequence (artificially synthesized oligo)
2C19-3-F-wt-3-IMS AGCACCCCCTGGATCCAGGTAAGGCCAAGTTTTTTGCTTC (SEQ ID NO:7)
The boxed region corresponds to the probe sequence.

[0035]

A result is shown in Figure 2. Figure 2 shows the curve without amending the measured value. Even in the case of perfect match, the rapid fall of fluorescence intensity was observed, and it was proved that the presumption in Example 1 was correct.

[Figure 1]



[Figure 2]